

SAMPLE ARRAYS AND HIGH-THROUGHPUT TESTING THEREOF TO DETECT
INTERACTIONS

5 This application is a continuation-in-part of Ser. No. 09/540,462 filed March 31, 2000, which claims the benefit of U.S. Provisional Application Nos. 60/146,019, filed July 28, 1999 and 60/127,755, filed April 5, 1999, the entire contents of which continuation-in-part application and provisional applications are incorporated herein by reference. This application also claims the priority benefit of U.S. Provisional Application No. 60/146,019, filed July 28, 1999.

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Field of the Invention

15 This invention is directed to the generation and analysis of data concerning multi-component chemical compositions, in particular, pharmaceutical or other formulations. More specifically, the invention is directed to methods, systems, and devices for high throughput measuring and testing of samples for optimization of sample properties and discovery of new compositions.

Background of the Invention

20 Discovery of pharmaceutical formulations that optimize bioavailability and duration of action of the pharmaceutical and minimize undesirable properties is an important part of pharmaceutical development and research. Pharmaceuticals are rarely distributed as pure compounds because of problems with, among others, stability, solubility, and bioavailability. In most cases, pharmaceuticals are administered in a pharmaceutical formulation comprising the active ingredients and excipients. It is well documented that
25 physical and chemical properties, such as stability, solubility, dissolution, permeability, and partitioning of most pharmaceuticals are directly related to the medium in which they are administered. This is because the medium affects the physical and chemical and chemical environment of the active ingredient, *e.g.*, a pharmaceutical. The physical and chemical properties of drug-in-formulation mixtures are directly related to pharmacological and
30 pharmacokinetic properties, such as absorption, bioavailability, metabolic profile, toxicity, and potency. Such effects are caused by physical and chemical interactions between the excipients and the pharmaceutical and/or physical and chemical interactions between the excipients themselves. Other properties influenced by the formulation in which a pharmaceutical is administered include mechanical properties, such as compressibility,

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compactability, and flow characteristics and sensory properties, such as taste, smell, and color.

Thus the goal of formulation development is to discover formulations that optimize desired characteristics of the pharmaceutical, such as stability, solubility, and bioavailability of a pharmaceutical under the conditions that it is administered. This is normally a tedious process, where each variable is separately assessed, at several points over a range of conditions or combinations. For example, if the formulation contains a pharmaceutical characterized by poor solubility, the solubility of the pharmaceutical in a range of salt concentrations; pHs; excipients; and pharmaceutical concentrations must be prepared and tested to find interactions between the pharmaceutical and excipients or interactions between excipients that affect the pharmaceutical's solubility. While some general rules exist, the effect of excipients and combinations of excipients on the physical and chemical properties of the pharmaceutical are not easily predicted. Moreover, there are over 3,000 excipients to choose from when designing pharmaceutical formulations, each having differing degrees and types of interactions with each other and with the pharmaceutical. Because of the many variables involved, industry does not have the time or resources to identify, measure, or exploit interactions between excipients and pharmaceuticals and thus cannot provide optimized pharmaceutical formulations tailored to the particular pharmaceutical. Such work would require testing hundreds to thousands of samples a day. Assuming three hundred substances are to be tested for efficacy as excipients in a pharmaceutical formulation, even with no variations in concentrations and no physical or chemical property variations, the number of possible combinations is enormous: when two of the substances are selected, there are 44,850 possible combinations, for three components there are 4,455,100 combinations, and for four components, there are 330,791,175 possible combinations. The complexity is increased when the relative ratio of each component is considered. Unfortunately, technologies that can make many pharmaceutical-excipient combinations at the same time, then automatically feed each combination into a system for identifying the combinations that have optimized properties are not known. Today, since it is more cost effective, most pharmaceuticals are distributed and administered in the standard, un-optimized formulations, *see e.g., Allen's Compounded Formulations: U.S. Pharmacists Collection 1995 to 1998*, ed. Loyd Allen.

Unfortunately, present day pharmaceutical formulation research and development, still relies on a select few excipients and retro-fits the active ingredients into well-known oral or parenteral formulation systems. This invention resists the traditional approach.

The need to provide optimized formulations is not limited to formulations wherein the active component is a pharmaceutical. Similar problems are encountered for administering dietary supplements, alternative medicines, nutraceuticals, sensory compounds, agrochemicals, and consumer and industrial product formulations. For example, similar to a pharmaceutical formulation, a vitamin formulation can be characterized by poor stability, solubility, bioavailability, taste, or smell. In another example, industrial product formulations, such as bleaching agents for paper mills can benefit by reformulation for higher stability so that the activity is not diminished during shipment.

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Summary of the Invention

The invention relates to high-throughput methods to prepare a large number of component combinations, at varying concentrations and identities, at the same time, and high-throughput methods to test each combination. Such methods allow detection or measurement of interactions between inactive components and active components; between multiple inactive components; or between multiple active components. Such methods also allow detection of lack of interactions between inactive components and active components; between multiple inactive components; or between multiple active components. The invention is particularly suited for making a large number of pharmaceutical-excipient combinations, then rapidly testing each combination to detect or measure interactions or to detect lack of interactions between excipients and the pharmaceutical; between excipients; or between multiple pharmaceuticals. Once such interactions or lack of interactions are identified, they can be exploited to develop optimized formulations for pharmaceutical administration.

The invention thus encompasses the high-throughput testing of pharmaceutical formulations in order to determine the overall optimal formulation for any particular ingredient, or to optimize any particular desired property or results, *e.g.*, bioavailability, potency, release, stability, and the like; or both. To applicant's knowledge, a systematic, high-throughput method for formulation generation, screening, testing, and analysis, has not been published prior to this invention. Moreover, an automated system for the generation, screening, and testing of such formulations is encompassed by this invention. Finally, computerized analysis of such data is encompassed by this invention. Specific embodiments of this invention are described in detail below.

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In one embodiment, the invention concerns an array of samples, each sample comprising a component-in-common and at least one additional component, wherein each sample differs from any other sample with respect to at least one of:

- (i) the identity of the additional component,
- 5 (ii) the ratio of the component-in-common to the additional component;
or
- (iii) the physical state of the component-in-common.

Component-in-common means that the component is present in every sample. Preferably, the component-in-common is an active component, more preferably, a pharmaceutical,
10 dietary supplement, alternative medicine, nutraceutical, sensory compound, agrochemical, the active component of a consumer product formulation, or the active component of an industrial product formulation. The samples and components can be in the form of solids, liquids, gels, foams, pastes, ointments, triturates, suspensions, or emulsions.

In another embodiment, the invention concerns a method to measure or detect an
15 interaction between components, comprising:

- (a) preparing an array of samples, each sample comprising a component-in-common and at least one additional component, wherein each sample differs from any other sample with respect to at least one of:
 - (i) the identity of the additional component,
 - 20 (ii) the ratio of the component-in-common to the additional component,
or
 - (iii) the physical state of the component-in-common; and
- (b) testing each sample for one or more properties.

In yet another embodiment, the invention concerns a method to measure or detect an
25 interaction between components, comprising:

- (a) preparing an array of samples, each sample comprising at least two components, wherein each sample differs from any other sample with respect to the identity of the components; the samples may further differ with respect to the ratio of the components, or the physical state of the components; and
30 (b) testing each sample for one or more properties.

In this embodiment, the samples do not have a component-in-common. The method is useful for testing mixtures of components, such as chemical fragrances, where each component has a different identity or chemical formula.

Preferably the samples are prepared, tested, and analyzed automatically and the data
35 stored and/or analyzed by a computer. Preferably, the component-in-common is an active

component, more preferably, a pharmaceutical, dietary supplement, alternative medicine, nutraceutical, sensory compound, agrochemical, the active component of a consumer product formulation, or the active component of an industrial product formulation. Most preferably, the component-in-common is a pharmaceutical. The samples and components
5 can be in the form of solids, liquids, gels, foams, pastes, ointments, triturates, suspensions, or emulsions.

In another embodiment, the invention concerns a method for testing or optimizing one or more properties of a formulation of an active-component, comprising:

- 10 (a) preparing an array of samples, each sample comprising the active component and at least one additional component, wherein each sample differs from any other sample with respect to at least one of:
- (i) the identity of the additional component,
 - (ii) the ratio of the active component to the additional component, or
 - (iii) the physical state of the active component;
- 15 (b) testing each sample for at least one property to generate a property-result for each sample; and
- (c) comparing the property-result generated for each sample to a baseline or a control for said property to generate a comparison result for the sample.

Preferably the samples are prepared, tested, and analyzed automatically and the data
20 stored and/or analyzed by a computer. Preferably, the active component is a pharmaceutical, dietary supplement, alternative medicine, nutraceutical, sensory compound, agrochemical, the active component of a consumer product formulation, or the active component of an industrial product formulation. Most preferably, the active component is a pharmaceutical. The samples and components can be in the form of solids, liquids, gels,
25 foams, pastes, ointments, triturates, suspensions, or emulsions.

In still another embodiment, the invention concerns a system to measure or detect an interaction between components, comprising:

- 30 (a) an array of samples, each sample comprising a component-in-common and at least one additional component, wherein each sample differs from any other sample with respect to at least one of:
- (i) the identity of the additional component,
 - (ii) the ratio of the component-in-common to the additional component;
 - or
 - (iii) the physical state of the component-in-common; and
- 35 (b) a sample tester to test each sample for one or more properties

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Preferably, the component-in-common is a pharmaceutical, dietary supplement, alternative medicine, nutraceutical, sensory compound, agrochemical, the active component of a consumer product formulation, or the active component of an industrial product formulation. Most preferably, the component-in-common is a pharmaceutical. The samples
5 and components can be in the form of solids, liquids, gels, foams, pastes, ointments, triturates, suspensions, or emulsions.

These and other features, aspects, and advantages of the invention will become better understood with reference to the following detailed description, examples, and appended claims.

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Brief Description of the Drawings

Figure 1 is a schematic of the method for preparing an array of samples, processing the samples, analyzing the samples for one or more properties, collecting and storing the data, analyzing the data, and detecting or measuring an interaction or detecting a lack of an
15 interaction.

Figures 2A and 2B is a more detailed schematic of a process to formulate and analyze multiple samples, for properties such as solubility (UV-VIS HPLC) and estimated oral absorbance, wherein Figure 2A is a schematic of the process wherein solids are deposited in sample wells in the array, then reconstituted and tested; and Figure 2B is a
20 schematic of the process wherein liquids are deposited into an array, dried, reconstituted and then separated into liquids and solids and tested.

Figure 3A is a graph of the solubility (absorbance) of 3,500 unique formulations containing griseofulvin with various excipients in water. Figure 3B is a graph of the data in Figure 3A plotted to show standard deviations for each of the unique formulations.

25 Figure 4 is a graph comparing solubility (absorbance) of the commercially available pharmaceutical with five lead formulations (TPI-1 to TPI-5).

Figure 5 is a graph of the ratio of the solubility of various reformulations of one of the lead formulations, TPI-3, reformulated with only one or two of the three excipients shown in relative ratios in the accompanying "pie". Figure 6 is a graph of the ratio of the
30 solubility of various reformulations of a lead formulation, TPI-1, comparing the effect of reformulating the formulation with one or two of the three excipients in the lead formulation, demonstrating that some excipients actually decrease solubility.

Figure 7 is a graph of the ratio of the solubility of various reformulations of one lead formulation, TPI-2, showing the effect of reformulating the formulation with one or two of

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the three excipients in the lead formulation, demonstrating that some excipients have a synergistic effect on solubility.

Figure 8 is a graph comparing rates of dissolution and equilibrium solubilities for TPI-2 and griseofulvin, showing TPI-2 having a higher rate of dissolution as well as a higher equilibrium solubility compared to the griseofulvin.

Detailed Description of the Invention

As used herein, the term "array" means a plurality of samples associated under a common experiment, wherein each of the samples comprises at least two components, one of the components being a component-in-common. The term "component-in-common" simply means a particular component that is present in every sample of the array, with the exception of negative controls. The array is designed to provide a data set, analysis of which allows detection or measurement of interactions (including lack of interactions) between the component-in-common and the other component. Each sample in the array differs from any other sample in the array with respect to at least one of:

- (i) the identity of the additional component,
- (ii) the ratio of the component-in-common to the additional component;
or
- (iii) the physical state of the component-in-common.

An array can comprise 24, 36, 48, 96, or more samples, preferably 1000 or more samples, more preferably, 10,000 or more samples. An array is typically comprised of one or more sub-arrays. For example, a sub-array can be a 96-well plate of sample wells.

As used herein, the term "sample" means a mixture of a component-in-common and one or more additional components. Preferably a sample comprises 2 or more additional components, more preferably, 3 or more additional components. In general, a sample will comprise one component-in-common but can comprise multiple components in common. A sample can be present in any container or holder or in or on any material or surface, the only requirement is that the samples be located at separate sites. Preferably, samples are contained in sample wells, for example, a 24, 36, 48, or 96 well plates (or filter plates) of volume 250 ul available from Millipore, Bedford, MA. The sample can comprise less than about 100 milligrams of the component-in-common, preferably, less than about 1 milligram, more preferably, less than about 100 micrograms, and even more preferably, less than 100 nanograms. Preferably, the sample has a total volume of 150-200 ul. Preferably a sample

comprises 2 or more additional components, more preferably, 3 or more additional components.

According to the invention described herein, the "physical state" of a component is initially defined by whether the component is a liquid or a solid. If the component is a solid, the physical state is further defined by the particle size and whether the component is crystalline or amorphous. If the component is crystalline, the physical state is further divided into: (1) whether the crystal matrix includes a co-adduct or whether the crystal matrix originally included a co-adduct, but the co-adduct was removed leaving behind a vacancy; (2) crystal habit; (3) morphology, *i.e.*, crystal habit and size distribution; and (4) internal structure (polymorphism). In a co-adduct, the crystal matrix can include either a stoichiometric or non-stoichiometric amount of the adduct, for example, a crystallization solvent or water, *i.e.*, a solvate or a hydrate. Non-stoichiometric solvates and hydrates include inclusions or clathrates, that is, where a solvent or water is trapped at random intervals within the crystal matrix, for example, in channels. A stoichiometric solvate or hydrate is where a crystal matrix includes a solvent or water at specific sites in a specific ratio. That is, the solvent or water molecule is part of the crystal matrix in a defined arrangement. Additionally, the physical state of a crystal matrix can change by removing a co-adduct, originally present in the crystal matrix. For example, if a solvent or water is removed from a solvate or a hydrate, a hole will be formed within the crystal matrix, thereby forming a new physical state. The crystal habit is the description of the outer appearance of an individual crystal, for example, a crystal may have a cubic, tetragonal, orthorhombic, monoclinic, triclinic, rhomboidal, or hexagonal shape. The processing characteristics are affected by crystal habit. The internal structure of a crystal refers to the crystalline form or polymorphism. A given compound may exist as different polymorphs, that is, distinct crystalline species. In general, different polymorphs of a given compound are as different in structure and properties as the crystals of two different compounds. Solubility, melting point, density, hardness, crystal shape, optical and electrical properties, vapor pressure, and stability, *etc.* all vary with the polymorphic form.

When referring to an interaction between components, an "interaction" means that the components as a mixture display a property (*e.g.*, the ability to solubilize a specific pharmaceutical) of a different magnitude or value than the same property displayed by each component in isolation. Interactions between components will affect the properties of samples. Merely for example, a particular combination and ratio of excipients can interact such that the combination has a high solubilizing power for a particular pharmaceutical.

Once such an interaction is detected, it can be exploited to develop enhanced formulations for the pharmaceutical.

As used herein, the term "component" means any substance. A component can be active or inactive. As used herein, the term "active component" means a substance that imparts the primary utility to a formulation when the formulation is used for its intended purpose. Examples of active components include pharmaceuticals, dietary supplements, alternative medicines, nutraceuticals, sensory compounds, agrochemicals, the active component of a consumer product formulation, and the active component of an industrial product formulation. As used herein, an "inactive component" means a component that is useful or potentially useful to serve in a formulation for administration of an active component, but does not significantly share in the active properties of the active component. Examples of suitable inactive components include, but are not limited to, excipients, solvents, diluents, stabilizers and combinations thereof.

Preferably, the samples of an array comprise an active component-in-common and inactive components. A number of permutations are available to the skilled artisan, for example, when the active component is a pharmaceutical, dietary supplement, alternative medicine, or nutraceutical, the preferred inactive components are excipients. When the active component is a sensory compound, such as a fragrance or flavor, the inactive components are preferably those inactive (non-sensory) substances or ingredients known in the art for administration of sensory compounds. When the active component is an agrochemical, preferably the inactive components are those inactive substances routinely used in the art to administer agrochemicals. When the active component is associated with a consumer or an industrial product formulation, the inactive components are preferably inactive substances known in the art to deliver such active components.

As used herein, the term "assaying agent" means a method, biological material, or reagent, such as an enzyme or cell line, useful for measuring the properties of a sample.

As used herein, the term "formulation" means a composition comprising a predefined ratio of one or more active components and one or more inactive components. A formulation is used as directed to administer the active component.

As used herein, the term "administer" means the act of delivering or applying an active component for its intended use via a formulation. For example, administration of pharmaceuticals, dietary supplements, alternative medicines, and nutraceuticals includes, but is not limited to, oral consumption, intravenous injection, and topical application.

Administration of agrochemical includes, but is not limited to, crop spraying and dusting. Administration of sensory compounds includes, but is not limited to, applying perfumes and

deodorants to the human body or eating a food or candy that has been supplemented by a flavor material. Administration of consumer and industrial product formulations means applying or simply using the product as directed. For example, administering a paint means applying the paint to a surface with a paint brush and administering a lubricant means
5 applying the lubricant to a surface where lubrication is desired.

According to the invention, the ratio of the component-in-common and to a particular additional component will differ between samples when the ratios thereof are intentionally varied to induce a measurable change in the sample's properties.

As used herein, the term "property" means a physical or chemical characteristic of a
10 sample. Preferred properties are those that relate to the efficacy, safety, stability, or utility of formulations before or after administration. For example, regarding pharmaceutical, dietary supplement, alternative medicine, and nutraceutical formulations, properties include physical properties, such as rheology, friability, stability, solubility, dissolution, permeability, and partitioning; mechanical properties, such as compressibility,
15 compactability, and flow characteristics; sensory properties, such as mouth feel, appearance, texture, color, taste, and smell; and properties that affect the utility, such as absorption, bioavailability, toxicity, metabolic profile, potency, rate-of-release, and rate-of-dispersion. Optimizing physical, sensory, and utility properties can result in a lowered required dose for the same therapeutic effect potentially with fewer side reactions, thereby improving patient
20 compliance.

An array comprises at least two samples and preferably comprises 24, 36, 48, 72 or more samples, more preferably 96 or more, still more preferably 1000 or more, most preferably 10,000 or more samples. The samples are located at separate sites and can be confined in any container or holder, absorbed into a suitable material, or present at separate
25 sites on a flat surface. Preferably, the samples are contained in sample wells. The sample wells can be of any dimensions or volume. Preferably, the sample wells have a volume with a range of 200 to 300 μ l, more preferably, 250 μ l. Arrays can be prepared by adding the component-in-common and the additional component(s) to the sample wells. The component-in-common is chosen by the skilled artisan according to the interaction to be
30 measured or identified. Preferably, the component-in-common is an active component (*i.e.*, an active component-in-common), more preferably, a pharmaceutical (*i.e.*, a pharmaceutical-in-common). But in some cases, the component-in-common is an inactive component, for example, where an array is designed to detect or measure an interaction between a particular excipient (an excipient-in-common) and other excipients. Active
35 components and inactive components can be chosen from known lists of substances

published in the literature or a component can be a newly discovered substance. Preferably, the inactive components are already known in the art for administration of the class of active component under study. For example, when the component-in-common is a pharmaceutical, the inactive components can be chosen from lists of known excipients.

5 For each sample in an array, the component-in-common and each component is in a particular ratio. The ratios of the component-in-common to the additional components are readily varied from sample to sample by the skilled artisan according to the component-in-common's identity and the information that the array is designed to provide.

10 Preferably, the sample components are mixed to obtain a homogeneous solution or suspension. One of skill in the art will know how to add and mix the components of each sample based on the particular study. The components can be added and mixed either manually or via automation.

15 Preferably the components are added to the sample wells and mixed automatically. "Automated" refers to samples prepared by using software and robotics to add and mix the components. After adding and mixing the components to the sample wells, the samples may be processed by well known techniques, such as heating, filtration, and lyophilization. One of skill in the art will know how to process the sample according to the properties being tested. The samples can be processed individually or as a group, preferably, as a group.

20 According to the methods of the invention, each sample in the array is tested or assayed for a particular property to provide a data set. The samples can be tested by a variety of known methods depending on the components and the property in question. The property can just be detected or the property can be measured to provide a value or magnitude for it. The value or magnitude of the property can be compared to a control or standard value to assess whether the sample's components are interacting or if the sample has potential to serve as a formulation for administering an active component. For example, when testing an array of samples—each sample comprising the same known drug but different excipients—to find the combination of excipients in which the drug displays the highest solubility, the solubility of the drug in each formulation may be compared to a control or standard value for the solubility. For instance, the solubility of the drug in each sample can be compared to the solubility of the drug in a commercial formulation or to the solubility of the drug in isolation.

Pharmaceuticals, Dietary Supplements, Alternative Medicines, and Nutraceuticals

The invention described herein is useful to detect or measure interactions between pharmaceuticals, dietary supplements, alternative medicines, or nutraceuticals and excipients thereby allowing development of formulations thereof with optimal properties.

In a one embodiment, the invention concerns an array of samples, each sample comprising a component-in-common is a pharmaceutical, a dietary supplement, an alternative medicine, or a nutraceutical and at least one additional component, wherein each sample differs from any other sample with respect to at least one of:

- (i) the identity of the additional component,
- (ii) the ratio of the component-in-common to the additional component;
- or
- (iii) the physical state of the component-in-common.

As used herein, the term "pharmaceutical" means any substance that has a therapeutic, disease preventive, diagnostic, or prophylactic effect when administered to an animal or a human. The term pharmaceutical includes prescription drugs and over the counter drugs. Pharmaceuticals suitable for use in the invention include all those known or to be developed.

Examples of suitable pharmaceuticals include, but are not limited to, cardiovascular pharmaceuticals, such as amlodipine besylate, losartan potassium, irbesartan, diltiazem hydrochloride, clopidogrel bisulfate, digoxin, abciximab, furosemide, amiodarone hydrochloride, beraprost, tocopheryl nicotinate; anti-infective components, such as amoxicillin, clavulanate potassium, azithromycin, itraconazole, acyclovir, fluconazole, terbinafine hydrochloride, erythromycin ethylsuccinate, and acetyl sulfisoxazole; psychotherapeutic components, such as sertaline hydrochloride, vanlafaxine, bupropion hydrochloride, olanzapine, buspirone hydrochloride, alprazolam, methylphenidate hydrochloride, fluvoxamine maleate, and ergoloid mesylates; gastrointestinal products, such as lansoprazole, ranitidine hydrochloride, famotidine, ondansetron hydrochloride, granisetron hydrochloride, sulfasalazine, and infliximab; respiratory therapies, such as loratadine, fexofenadine hydrochloride, cetirizine hydrochloride, fluticasone propionate, salmeterol xinafoate, and budesonide; cholesterol reducers, such as atorvastatin calcium, lovastatin, bezafibrate, ciprofibrate, and gemfibrozil; cancer and cancer-related therapies, such as paclitaxel, carboplatin, tamoxifen citrate, docetaxel, epirubicin hydrochloride, leuprolide acetate, bicalutamide, goserelin acetate implant, irinotecan hydrochloride, gemcitabine hydrochloride, and sargramostim; blood modifiers, such as epoetin alfa, enoxaparin sodium, and antihemophilic factor; antiarthritic components, such as celecoxib, nabumetone, misoprostol, and rofecoxib; AIDS and AIDS-related pharmaceuticals, such as

lamivudine, indinavir sulfate, stavudine, and lamivudine; diabetes and diabetes-related therapies, such as metformin hydrochloride, troglitazone, and acarbose; biologicals, such as hepatitis B vaccine, and hepatitis A vaccine; hormones, such as estradiol, mycophenolate mofetil, and methylprednisolone; analgesics, such as tramadol hydrochloride, fentanyl, metamizole, ketoprofen, morphine sulfate, lysine acetylsalicylate, ketoralac tromethamine, morphine, loxoprofen sodium, and ibuprofen; dermatological products, such as isotretinoin and clindamycin phosphate; anesthetics, such as propofol, midazolam hydrochloride, and lidocaine hydrochloride; migraine therapies, such as sumatriptan succinate, zolmitriptan, and rizatriptan benzoate; sedatives and hypnotics, such as zolpidem, zolpidem tartrate, triazolam, and hycosine butylbromide; imaging components, such as iohexol, technetium, TC99M, sestamibi, iomeprol, gadodiamide, ioversol, and iopromide; and diagnostic and contrast components, such as alsactide, americium, betazole, histamine, mannitol, metyrapone, petagastrin, phentolamine, radioactive B₁₂, gadodiamide, gadopentetic acid, gadoteridol, and perflubron. Other pharmaceuticals for use in the invention include those listed in Table 1 below, which suffer from problems that could be mitigated by developing new administration formulations according to the arrays and methods of the invention.

TABLE 1: Exemplary Pharmaceuticals

Brand Name	Chemical	Properties
SANDIMMUNE	cyclosporin	Poor absorption due to its low water solubility.
TAXOL	paclitaxel	Poor absorption due to its low water solubility.
VIAGRA	sildenafil citrate	Poor absorption due to its low water solubility.
NORVIR	ritonavir	Can undergo a polymorphic shift during shipping and storage.
FULVICIN	griseofulvin	Poor absorption due to its low water solubility.
FORTOVASE	saquinavir	Poor absorption due to its low water solubility.

Still other examples of suitable pharmaceuticals are listed in 2000 *Med Ad News* 19:56-60 and *The Physicians Desk Reference*, 53rd edition, 792-796, Medical Economics Company (1999), both of which are incorporated herein by reference.

Examples of suitable veterinary pharmaceuticals include, but are not limited to, vaccines, antibiotics, growth enhancing components, and dewormers. Other examples of suitable veterinary pharmaceuticals are listed in *The Merck Veterinary Manual*, 8th ed.,

Merck and Co., Inc., Rahway, NJ, 1998; (1997); *The Encyclopedia of Chemical Technology*, 24 Kirk-Othmer (4th ed. at 826); and *Veterinary Drugs in ECT* 2nd ed., Vol 21, by A.L. Shore and R.J. Magee, American Cyanamid Co.

As used herein, the term "dietary supplement" means a non-caloric or insignificant-caloric substance administered to an animal or a human to provide a nutritional benefit or a non-caloric or insignificant-caloric substance administered in a food to impart the food with an aesthetic, textural, stabilizing, or nutritional benefit. Dietary supplements include, but are not limited to, fat binders, such as caducean; fish oils; plant extracts, such as garlic and pepper extracts; vitamins and minerals; food additives, such as preservatives, acidulents, anticaking components, antifoaming components, antioxidants, bulking components, coloring components, curing components, dietary fibers, emulsifiers, enzymes, firming components, humectants, leavening components, lubricants, non-nutritive sweeteners, food-grade solvents, thickeners; fat substitutes, and flavor enhancers; and dietary aids, such as appetite suppressants. Examples of suitable dietary supplements are listed in (1994) *The Encyclopedia of Chemical Technology*, 11 Kirk-Othmer (4th ed. at 805-833). Examples of suitable vitamins are listed in (1998) *The Encyclopedia of Chemical Technology*, 25 Kirk-Othmer (4th ed. at 1) and *Goodman & Gilman's: The Pharmacological Basis of Therapeutics*, 9th Edition, eds. Joel G. Harman and Lee E. Limbird, McGraw-Hill, 1996 p.1547, both of which are incorporated by reference herein. Examples of suitable minerals are listed in *The Encyclopedia of Chemical Technology*, 16 Kirk-Othmer (4th ed. at 746) and "Mineral Nutrients" in *ECT* 3rd ed., Vol 15, pp. 570-603, by C.L. Rollinson and M.G. Enig, University of Maryland, both of which are incorporated herein by reference

As used herein, the term "alternative medicine" means a substance, preferably a natural substance, such as a herb or an herb extract or concentrate, administered to a subject or a patient for the treatment of disease or for general health or well being, wherein the substance does not require approval by the FDA. Examples of suitable alternative medicines include, but are not limited to, ginkgo biloba, ginseng root, valerian root, oak bark, kava kava, echinacea, *harpagophyti* radix, others are listed in *The Complete German Commission E Monographs: Therapeutic Guide to Herbal Medicine*, Mark Blumenthal et al. eds., Integrative Medicine Communications 1998, incorporated by reference herein.

As used herein the term "nutraceutical" means a food or food product having both caloric value and pharmaceutical or therapeutic properties. Example of nutraceuticals include garlic, pepper, brans and fibers, and health drinks. Examples of suitable Nutraceuticals are listed in M.C. Linder, ed. *Nutritional Biochemistry and Metabolism with*

Clinical Applications, Elsevier, New York, 1985; Pszczola *et al.*, 1998 *Food technology* 52:30-37 and Shukla *et al.*, 1992 *Cereal Foods World* 37:665-666.

Preferably, when the component-in-common is a pharmaceutical, a dietary supplement, an alternative medicine, or a nutraceutical, the additional component(s) are excipients. As used herein, the term "excipient" means the inactive substances used to formulate pharmaceuticals as a result of processing or manufacture or used by those of skill in the art to formulate pharmaceuticals, dietary supplements, alternative medicines, and nutraceuticals for administration to animals or humans. Preferably, excipients are approved for or considered to be safe for human and animal administration. Examples of suitable excipients include, but are not limited to, acidulents, such as lactic acid, hydrochloric acid, and tartaric acid; solubilizing components, such as non-ionic, cationic, and anionic surfactants; absorbents, such as bentonite, cellulose, and kaolin; alkalizing components, such as diethanolamine, potassium citrate, and sodium bicarbonate; anticaking components, such as calcium phosphate tribasic, magnesium trisilicate, and talc; antimicrobial components, such as benzoic acid, sorbic acid, benzyl alcohol, benzethonium chloride, bronopol, alkyl parabens, cetrimide, phenol, phenylmercuric acetate, thimerosal, and phenoxyethanol; antioxidants, such as ascorbic acid, alpha tocopherol, propyl gallate, and sodium metabisulfite; binders, such as acacia, alginic acid, carboxymethyl cellulose, hydroxyethyl cellulose; dextrin, gelatin, guar gum, magnesium aluminum silicate, maltodextrin, povidone, starch, vegetable oil, and zein; buffering components, such as sodium phosphate, malic acid, and potassium citrate; chelating components, such as EDTA, malic acid, and maltol; coating components, such as adjunct sugar, cetyl alcohol, polyvinyl alcohol, carnauba wax, lactose maltitol, titanium dioxide; controlled release vehicles, such as microcrystalline wax, white wax, and yellow wax; desiccants, such as calcium sulfate; detergents, such as sodium lauryl sulfate; diluents, such as calcium phosphate, sorbitol, starch, talc, lactitol, polymethacrylates, sodium chloride, and glyceryl palmitostearate; disintegrants, such as colloidal silicon dioxide, croscarmellose sodium, magnesium aluminum silicate, potassium polacrilin, and sodium starch glycolate; dispersing components, such as poloxamer 386, and polyoxyethylene fatty esters (polysorbates); emollients, such as cetearyl alcohol, lanolin, mineral oil, petrolatum, cholesterol, isopropyl myristate, and lecithin; emulsifying components, such as anionic emulsifying wax, monoethanolamine, and medium chain triglycerides; flavoring components, such as ethyl maltol, ethyl vanillin, fumaric acid, malic acid, maltol, and menthol; humectants, such as glycerin, propylene glycol, sorbitol, and triacetin; lubricants, such as calcium stearate, canola oil, glyceryl palmitostearate, magnesium oxide, poloxamer, sodium benzoate, stearic

acid, and zinc stearate; solvents, such as alcohols, benzyl phenylformate, vegetable oils, diethyl phthalate, ethyl oleate, glycerol, glycofurol, for indigo carmine, polyethylene glycol, for sunset yellow, for tartazine, triacetin; stabilizing components, such as cyclodextrins, albumin, xanthan gum; and tonicity components, such as glycerol, dextrose, potassium chloride, and sodium chloride; and mixture thereof. Excipients include those alter rate of absorption, bioavailability, or other pharmacokinetic properties of pharmaceuticals, dietary supplements, alternative medicines, or nutraceuticals. Other examples of suitable excipients, such as binders and fillers are listed in *Remington's Pharmaceutical Sciences*, 18th Edition, ed. Alfonso Gennaro, Mack Publishing Co. Easton, PA, 1995 and Handbook of Pharmaceutical Excipients, 3rd Edition, ed. Arthur H. Kibbe, American Pharmaceutical Association, Washington D.C. 2000, both of which are incorporated herein by reference.

The definition of the term "excipient", as used herein, also includes solvents. Aqueous solvents can be used to make mixtures, suspensions, and matrices formed of water soluble polymers. Organic solvents will typically be used to dissolve hydrophobic and some hydrophilic polymers. Preferred organic solvents are volatile or have a relatively low boiling point or can be removed under vacuum and which are non-toxic or acceptable for administration to humans in trace amounts, such as methylene chloride. Other solvents, such as ethyl acetate, ethanol, methanol, dimethyl formamide, acetone, acetonitrile, tetrahydrofuran, acetic acid, dimethyl sulfoxide, and chloroform, and mixture thereof, also may be used. Preferred solvents are those rated as class 3 residual solvents by the Food and Drug Administration, as published in the Federal Register vol. 62, number 85, pp. 24301-24309 (May 1997). Solvents for drugs that are administered parenterally or as a solution or suspension will more typically be distilled water, buffered saline, Lactated Ringer's or some other pharmaceutically acceptable carrier.

In one aspect of the embodiment concerning arrays of samples, wherein the component-in-common is selected from the group of pharmaceuticals, dietary supplements, alternative medicines, and nutraceuticals, the additional component is also selected from the group of pharmaceuticals, dietary supplements, alternative medicines, and nutraceuticals. That is, each sample can comprise multiple active components, wherein a particular active component is present in all the samples (*i.e.*, the component-in-common). An array of such samples can be used to detect favorable or synergistic interactions between pharmaceuticals, dietary supplements, alternative medicines, and nutraceuticals and other pharmaceuticals, dietary supplements, alternative medicines, and nutraceuticals. For instance, an array of samples, wherein each sample comprises the same pharmaceutical-in-common and each sample also comprises a different, additional component selected from the group of a

pharmaceutical, a dietary supplement, an alternative medicine, or a nutraceuticals can be used to identify particularly advantageous combinations of active components. Such advantageous combinations may be unexpected based on the properties of the components in isolation. An array of such multiple-active-component samples can also be used to find suitable excipient combinations to co-formulate two or more active component, *e.g.*, formulate two or more pharmaceuticals into a multiple dosage form. Such multiple-dosage forms can obviate the need for the patient to take multiple medications (polypharmacy), since the prescribed pharmaceuticals are conveniently contained in one formulation.

In another embodiment, the invention relates to a method to measure or detect an interaction between components, comprising:

- (a) preparing an array of samples, each sample comprising a component-in-common is a pharmaceutical, a dietary supplement, an alternative medicine, or a nutraceutical and at least one additional component, wherein each sample differs from any other sample with respect to at least one of:
 - (i) the identity of the additional component,
 - (ii) the ratio of the component-in-common to the additional component;or
 - (iii) the physical state of the component-in-common;
- (b) testing each sample for a property to generate a data set; and
- (c) analyzing the data set to measure or detect the interaction.

Preferably, the samples are tested for properties that relate to administration and pharmacokinetics of pharmaceuticals, dietary supplements, alternative medicines, or nutraceuticals. Preferred properties include, but are not limited to, physical properties, such as rheology, friability, stability, solubility, dissolution, permeability, and partitioning; mechanical properties, such as compressibility, compactability, and flow characteristics; sensory properties, such as mouth feel, appearance, texture, color, taste, and smell; and properties that affect the utility, such as absorption, bioavailability, toxicity, metabolic profile, potency, rate-of-release, and rate-of-dispersion. While some biological properties relate to *in vivo* performance of an active component, such as a pharmaceutical formulation, they can be measured by *in vitro* tests that can be extrapolated to *in vivo* performance.

Toxicity is the pharmaceutical formulations propensity to cause detrimental side effects when administered to a subject or patient. Toxicity includes hypersensitivity and allergic reactions. Potency is the activity that the formulation has for its intended purpose. Both of these biological properties can be measured by *in vitro* techniques, such as microbial assays. For a discussion of *in vitro* biological testing methods see *Remington's*

Pharmaceutical Sciences, 18th Edition, ed. Alfonso Gennaro, Mack Publishing Co. Easton, PA, 1995, pp.499-500, all three of which are incorporated herein by reference.

Absorption is the process of movement of an active component, such as a pharmaceutical from the site of application past the physiological barrier—for example, crossing through the gastrointestinal tract in the case of oral dosage; crossing through the skin and into the blood stream in the case of transdermal dosage; or crossing through the stratum corneum and into the dermis in the case of an intradermal dosage. Many factors determine the ease with which a pharmaceutical is absorbed, for example, the pharmaceutical's concentration, solubility, and permeation ability. While techniques exist to test each of these properties, some general tests are available to estimate absorption directly, for example, an Ussing chamber containing HT Caco-2/MS engineered cells as reported in Lennernas, H. 1998 *J. Pharm. Sci.* 87:403-410. For a detailed discussion of the theory of and methods for measuring absorption of pharmaceuticals see *Remington's Pharmaceutical Sciences*, 18th Edition, ed. Alfonso Gennaro, Mack Publishing Co. Easton, PA, 1995, pp. 710-714, incorporated herein by reference.

Solubility refers to the equilibrium solubility or steady state and is measured as weight component/volume solvent. When an active component, such as a pharmaceutical substance has an aqueous solubility of less than about 1 milligram/milliliter in the physiological pH range of 1-7, a potential bioavailability problem exists. Descriptive terms used to describe solubility given in parts of solvent for 1 part of solvent are: very soluble (<1 part); freely soluble (from 1 to 10 parts); soluble (from 10 to 30 parts); sparingly soluble (from 30 to 100 parts); slightly soluble (from 100 to 1,000 parts); very slightly soluble (from 1,000 to 10,000 parts); and insoluble (> 10,000 parts). For a discussion of solution and phase equilibria see *Remington's Pharmaceutical Sciences*, 18th Edition, ed. Alfonso Gennaro, Mack Publishing Co. Easton, PA, 1995, Ch. 16, incorporated herein by reference.

The solubility can be tested by mixing the sample with a test solvent and agitating the sample at a constant temperature until equilibrium is achieved. Equilibrium usually occurs upon agitating the samples for 6 to 24 hours. If the component is acidic or basic, its solubility can be influenced by pH and one of skill in the art will take such factors into consideration when testing the solubility properties of a sample. Once equilibrium has occurred, the sample can be tested to determine the amount of component dissolved using standard technology, such as mass spectroscopy, HPLC, UV spectroscopy, fluorescence spectroscopy, gas chromatography, optical density, or by colorimetry. For a discussion of the theory and methods of measuring solubility see Streng *et al.*, 1984 *J. Pharm. Sci.* 63:605; Kaplan 1972 *Drug Metab. Rev.* 1:15; and *Remington's Pharmaceutical Sciences*,

18th Edition, ed. Alfonso Gennaro, Mack Publishing Co. Easton, PA, 1995, pp.1456-1457, all three of which are incorporated herein by reference. For a discussion of heat of dissolution, pKa, and pH solubility profile effects and techniques for measurement thereof see Fiese *et al.*, in *The Theory and Practice of Industrial Pharmacy*, 3rd ed., Lachman L.; 5 Lieberman, H.A.; and Kanig, J.L. Eds., Lea and Febiger, Philadelphia, 1986 pp. 185-188, incorporated herein by reference.

Dissolution refers to the process by which a solid of only fair solubility enters into solution. Several factors affect dissolution such as solubility, particle size, crystalline state, and the presence of diluents, disintegrants, or other excipients. For a discussion of the 10 theory and methods of measuring dissolution see *Remington's Pharmaceutical Sciences*, 18th Edition, ed. Alfonso Gennaro, Mack Publishing Co. Easton, PA, 1995, Chapter 34, incorporated herein by reference.

Stability refers to the chemical and physical stability of the component during manufacturing, packaging, distribution, storage, and administration of the active- 15 component(s), to the formulation as a whole, or components thereof.

Chemical stability refers to resistance of the formulation to chemical reactions induced, for example, by heat, ultraviolet radiation, moisture, chemical reactions between components, or oxygen. Chemical stability also refers to a compound's ability to maintain a particular stereoisomeric form without conversion to another stereoisomeric form, *e.g.*, 20 optical activity. Well known methods for measuring chemical stability include mass spectroscopy, UV-VIS spectroscopy, polarimetry, chiral and non-chiral HPLC, chiral and non-chiral gas chromatography, and liquid chromatography-mass spectroscopy (LC-MS). In the case of surface discoloration due to oxidation or due to reaction of the active component with excipients or with itself, surface reflectance measurements can be more 25 sensitive than other assays. For a discussion of the theory and methods of measuring chemical stability see Xu *et al.*, *Stability-Indicating HPLC Methods for Drug Analysis* American Pharmaceutical Association, Washington D.C. 1999 and *Remington's Pharmaceutical Sciences*, 18th Edition, ed. Alfonso Gennaro, Mack Publishing Co. Easton, PA, 1995, pp. 1458-1460, both of which are incorporated herein by reference.

30 Physical stability refers to a formulation's ability to maintain its physical form, for example maintaining particle size; maintaining crystal or amorphous form; maintaining complexed form, such as hydrates and solvates; resistance to absorption of ambient moisture, *i.e.*, hygroscopicity; and maintaining of mechanical properties, such as compressibility and flow characteristics. Methods for measuring physical stability include 35 spectroscopy, sieving or testing, microscopy, sedimentation, stream scanning, and light

scattering. Polymorphic changes, for example, are usually detected by differential scanning calorimetry or quantitative infrared analysis. For a discussion of the theory and methods of measuring physical stability see Fiese *et al.*, in *The Theory and Practice of Industrial Pharmacy*, 3rd ed., Lachman L.; Lieberman, H.A.; and Kanig, J.L. Eds., Lea and Febiger, Philadelphia, 1986 pp. 193-194 and *Remington's Pharmaceutical Sciences*, 18th Edition, ed. Alfonso Gennaro, Mack Publishing Co. Easton, PA, 1995, pp. 1448-1451, both of which are incorporated herein by reference.

Permeability refers to the propensity of a component to pass across biological membranes. Biological membranes act as lipid barriers to most pharmaceuticals and permit the absorption of lipid-soluble substances by passive diffusion. Lipid-insoluble substances can pass the barrier only with considerable difficulty. An *in vitro* procedure for measuring permeability characteristics consists of an aqueous/organic-lipid layer/aqueous system. Another *in vitro* procedure is the everted sac technique using segments of rat small intestines. For a discussion of the theory and methods of measuring permeability see *Remington's Pharmaceutical Sciences*, 18th Edition, ed. Alfonso Gennaro, Mack Publishing Co. Easton, PA, 1995, pp. 1460-1461, incorporated herein by reference.

Partitioning refers to how a component distributes itself between two phases so that each phase becomes saturated. If the component is added to the immiscible solvent system in an amount insufficient to saturate the solutions, it will distribute between the solvents in a definite ratio. Understanding the partitioning effect enables one to estimate the site of absorption, for example, whether a component is absorbed in the stomach or small intestines. For a discussion of the theory and methods of measuring partitioning see Hansch *et al.*, 1972 *J. Pharm. Sci.* 61:1; Dressman *et al.*, 1984 *J. Pharm. Sci.* 73:1274; Suzuki *et al.*, 1970 *J. Pharm. Sci.* 59:644; and *Remington's Pharmaceutical Sciences*, 18th Edition, ed. Alfonso Gennaro, Mack Publishing Co. Easton, PA, 1995, pp. 1451-1452, all of which are incorporated herein by reference.

Metabolic profile or metabolism refers to conversion of a pharmaceutical, dietary supplement, alternative medicine, or nutraceutical to another chemical within a human or animal after administration. As soon as a pharmaceutical enters the body it becomes susceptible to a variety of enzymatic or chemical metabolic processes in the stomach, intestine, and liver as well as other areas of the body. Metabolism can occur at different sites in the body, formulations are especially important in optimizing, for example, transdermal, dermal, and gastric metabolism. Metabolism can occur by functional group changes, such as ring or side chain hydroxylation, nitro-group reduction, aldehyde oxidation, dealkylation, deamination, *etc.* or by conjugation, wherein the pharmaceutical

combines with a solubilizable group, such as glucuronic acid or glycine to form an excretable compound. Metabolism of an active component, such as a pharmaceutical, can be enhanced or retarded depending on the formulation in which the active component is administered. Although metabolism occurs within the body, it can be measured using a variety of *in vitro* assays. For example, certain oral pharmaceuticals, such as the penicillins, are undesirably metabolized through acid hydrolysis in the digestive tract. To estimate efficacy of a formulation for mitigating such metabolism and allowing the pharmaceutical to pass into the blood stream, a formulation comprising the pharmaceutical in question may be placed in a medium approximating the digestive medium and the rate or extent of hydrolysis measured by an appropriate analytical technique, such as HPLC. Similarly, for pharmaceuticals known to be metabolized by certain enzymes, the efficacy of a formulation for promoting or retarding metabolism can be tested by exposing the pharmaceutical formulation to the enzyme or a similar enzyme under appropriate conditions and measuring the rate of degradation. For a discussion of the theory and methods of measuring metabolism see *Remington's Pharmaceutical Sciences*, 18th Edition, ed. Alfonso Gennaro, Mack Publishing Co. Easton, PA, 1995, pp. 431, 742, 1665, 1753, and 1831, incorporated herein by reference.

Compressibility refers to a powder's capacity to decrease in volume under pressure, while compactability refers to its capacity to be compressed into a tablet of particular strength or hardness. When a powder undergoes compression, the powder particles adopt a more efficient packing order and upon further pressure undergo elastic or reversible deformation. If the force were to be removed during this phase, the powder would recover to the efficiently packed state. Further application of pressure results in compaction, *i.e.*, irreversible deformation of the powder. The compaction stage is very important in the manufacture of tablets. For tableting, the pharmaceutical-in-formulation mixture must be amenable to irreversible deformation (compaction) upon pressure application to a tablet hard enough to resist erosion and disintegration and strong enough to resist brittle fracture. See *Remington's Pharmaceutical Sciences*, 18th Edition, ed. Alfonso Gennaro, Mack Publishing Co. Easton, PA, 1995, pp. 1457-1458 and chapter 92 and Jones *et al.*, 1977 *Pharmazeutische Industrie*, 39:469, both of which are incorporated herein by reference herein. Numerous techniques to measure to evaluate compressibility and compactability are published, *e.g.*, see Rees *et al.*, 1987 *J. Pharm. Pharmacol.* 30:601 and Jones in Polermand ed: *Formulation and Preparation of Dosage Forms*, Elsevier, North Holland, 29, 1977.

Power flow characteristics refer to a bulk powder's ability to flow. Powders can be broadly classified as free flowing or cohesive. Flow characteristics can be influenced by

particle size, shape, and morphology as well as other factor such as density, electrostatic charge, the presence of absorbed air or moisture. Free flowing powders can be characterized by a simple flow-rate apparatus consisting of grounded metal tube from which the pharmaceutical flows through the orifice onto an electronic balance. For a discussion of measuring properties affecting flow characteristics see Kaye Chemical analysis: *Direct Characterization of Fine Particles*. Vol. 61, John Wiley and Sons, New York 1981; Sutton *et al.*, *Characterization of Powder Surfaces*, Academic Press, London, 1976, pp. 1,7, and 158; Hiestand, *et al.*, 1973 *J. Pharm. Sci.* 62:1513; and Hiestand, *et al.*, 1974 *J. Pharm. Sci.* 63:605, all of which are incorporated by reference herein.

10 Friability is an indicator of cohesiveness and hardness of a powdered solid-dosages forms, e.g., tablets, of pharmaceuticals, dietary supplements, alternative medicines, and nutraceuticals. Friability can be measured by well-known methods, such as with a Roche friabilitor. For a discussion of friability and methods for measuring see *Remington's Pharmaceutical Sciences*, 18th Edition, ed. Alfonso Gennaro, Mack Publishing Co. Easton, PA, 1995, pp. 1639-1640, incorporated herein by reference.

15 Rheology concerns deformation and flow of matter. For pharmaceuticals, dietary supplements, alternative medicines, nutraceuticals, consumer product formulation and industrial formulations, rheology relates to mechanical properties such adhesive strength, tackiness, and viscosity. Rheology is especially import in pharmaceutical applications of biopolymers and mucoadhesives. For example, in transdermal and dermal applications where a bioadhesive must adhere to the skin and later be removed without causing pain. Rheology is also important in industrial and consumer product formulations, such as polymers, adhesives, glues, gels, rubbers, inks, and plastics. Rheology can be measured by well-known methods, for a discussion see *Remington's Pharmaceutical Sciences*, 18th Edition, ed. Alfonso Gennaro, Mack Publishing Co. Easton, PA, 1995, Ch. 22, incorporated herein by reference.

20 Dispersion relates to the mechanical disintegration properties of solids and liquids into small particles and their distribution and dissolution in a fluid vehicle. Dispersion properties are especially important in pharmaceutical, dietary supplement, alternative medicine, and nutraceutical formulations. Dispersion properties of formulations can be enhanced by additives, such as disintegrants and lubricants. For a discussion of dispersion and its relationship to dissolution and disintegration and tests therefor see *Remington's Pharmaceutical Sciences*, 18th Edition, ed. Alfonso Gennaro, Mack Publishing Co. Easton, PA, 1995, pp. 595-596, incorporated herein by reference.

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Rate-of-release refers to the release of a pharmaceutical from a pharmaceutical formulation, thus presenting the pharmaceutical for absorption. Control of rate-of-release allows timed delivery of a dosage over an extended period or immediate surrender of the total dosage. Rate-of-release is intimately related to the formulation's properties, such as friability, dispersion, disintegration, pharmaceutical concentration, pharmaceutical-carrier interactions, particle size and type, pH, polarity, surface tension, and rheology, to name but a few. For a discussion of and assays to measure rate-of-release see, see *Chemical Aspects of Drug Delivery Systems*, eds. D.R. Karsa and R.A. Stephenson, The Royal Society of Chemistry, Cambridge, UK, 1996, incorporated herein by reference

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Sensory Materials

In a another embodiment, the invention relates to an array of samples, each sample comprising a sensory-material-in-common and at least one additional component, wherein each sample differs from any other sample with respect to at least one of:

- 15 (i) the identity of the additional component,
 (ii) the ratio of the sensory-material-in-common to the additional
 component; or
 (iii) the physical state of the sensory-material-in-common.

As used herein, the term "sensory-material" means any chemical or substance, known or to be developed, that is used to provide an olfactory or taste effect in a human or an animal, preferably, a fragrance material, a flavor material, or a spice. A sensory-material also includes any chemical or substance used to mask an odor or taste. Examples of suitable fragrances materials include, but are not limited to, musk materials, such as civetone, ambrettolide, ethylene brassylate, musk xylene, Tonalide®, and Glaxolide®; amber materials, such as ambrox, ambreinolide, and ambrinol; sandalwood materials, such as α -santalol, β -santalol, Sandalore®, and Bacdanol®; patchouli and woody materials, such as patchouli oil, patchouli alcohol, Timberol® and Polywood®; materials with floral odors, such as Givescione®, damascone, irones, linalool, Lilial®, Lilestralis®, and dihydrojasmonate. Other examples of suitable fragrance materials for use in the invention are listed in *Perfumes: Art, Science, Technology*, P.M. Muller ed. Elsevier, New York, 1991, incorporated herein by reference. Examples of suitable flavor materials include, but are not limited to, benzaldehyde, anethole, dimethyl sulfide, vanillin, methyl anthranilate, nootkatone, and cinnamyl acetate. Examples of suitable spices include but are not limited to allspice, tarrogon, clove, pepper, sage, thyme, and coriander. Other examples of suitable flavor materials and spices are listed in *Flavor and Fragrance Materials-1989*, Allured

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Publishing Corp. Wheaton, IL, 1989; Bauer and Garbe Common Flavor and Fragrance Materials, VCH Verlagsgesellschaft, Weinheim, 1985; and (1994) *The Encyclopedia of Chemical Technology*, 11 Kirk-Othmer (4th ed. at 1-61), all of which are incorporated by reference herein.

5 Preferred components for use with sensory-materials are those known in the art of fragrance and flavor compounding, for example, components used to make functional products, such as those used to formulate colognes and perfumes, skin cleansers, shower products, skin-care products, gels, sun screens, deodorants and antiperspirants, hair-care products and shampoos, and cosmetics. Other examples of suitable components are the
10 excipients listed above for use with pharmaceuticals as they can also be used to formulate formulations comprising sensory-materials. Other examples of suitable components for samples comprising sensory-materials are listed in *Perfumes: Art, Science, Technology*, P.M. Muller ed. Elsevier, New York, 1991 p. 338-345, 347-362, 40-42 and (1996) *The Encyclopedia of Chemical Technology*, 18 Kirk-Othmer (4th ed. at 171-201), both of which
15 are incorporated by reference herein. In one aspect of the embodiment concerning arrays of samples, wherein the component-in-common is a sensory-material, the additional component(s) are other sensory-materials. That is, each sample can comprise multiple sensory-materials, wherein a particular sensory-material is present in all the samples (sensory-material-in-common). An array of such samples can be used to detect favorable or
20 synergistic interactions between sensory-materials, for example, identification of a sensory-material combination that is particularly advantageous due to their interaction with each other. Such advantageous combinations can be unexpected based on the properties of the sensory-materials in isolation.

In another embodiment, the invention relates to a method to measure or detect an
25 interaction between a sensory-material and another component, comprising:

- (a) preparing an array of samples, each sample comprising a sensory-material-in-common and at least one additional component, wherein each sample differs from any other sample with respect to at least one of:
 - (i) the identity of the additional component,
 - 30 (ii) the ratio of the sensory-material-in-common to the additional component; or
 - (iii) the physical state of the sensory-material-in-common;
- (b) testing each sample for a property to generate a data set; and
- (c) analyzing the data set to measure or detect the interaction.

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Preferably, samples comprising sensory-materials are tested for properties related to their use in functional products, such as perfumes, air fresheners, deodorants, colognes, foods, candy, or fragranced or flavored pharmaceuticals. Preferred properties for sensory materials include strength and quality of the odor, substantivity (how long the odor lasts), rate of evaporation, solubility, partitioning, biodegradability, odor, taste, mouth feel, appearance, lack of odor, lack of taste, toxicity, potency, texture, color, appearance, or partitioning and physical and chemical stability. One of skill in the art can readily develop assays to measure such properties, for instance, the methods discussed above for measuring pharmaceutical formulation properties. For example, strength and quality of odor can be measured by simply smelling the sample or by neurosensory techniques, such as electronic noses, see *e.g.*, Matzger *et al.*, 2000 *J. Comb. Chem.* 2:301-304; Gibson *et al.*, 2000 *Chem. Ind. (London)* 8:287-289; Ormancey *et al.*, 1998 *Semin. Food Anal.* 3:77-84; Bain, H., *Measurement of Consumer Perceptions and Evaluation of odor as an Aid to Perfume Selection*, In ESOMAR Seminar on Research for Flavors and Fragrances, Lyon 1989, Esomar, Amsterdam, 1989, all four of which are incorporated herein by reference. Properties such as substantivity, rate of evaporation, solubility, partitioning, and physical and chemical stability can be measured by adaptation of the methods discussed above for pharmaceuticals.

20 Agrochemicals

In still another embodiment, the invention relates to an array of samples, each sample comprising an agrochemical-in-common and at least one additional component, wherein each sample differs from any other sample with respect to at least one of:

- (i) the identity of the additional component,
- 25 (ii) the ratio of the agrochemical-in-common to the additional component; or
- (iii) the physical state of the agrochemical-in-common.

As used herein, the term "agrochemical" means any substance known or to be developed that is used on the farm, yard, or in the house or living area to benefit gardens, crops, ornamental plants, shrubs, or vegetables or kill insects, plants, or fungi. Examples of suitable agrochemicals for use in the invention include pesticides, herbicides, fungicides, insect repellants, fertilizers, and growth enhancers. For a discussion of agrochemicals see *The Agrochemicals Handbook* (1987) 2nd Edition, Hartley and Kidd, editors: The Royal Society of Chemistry, Nottingham, England.

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Pesticides include chemicals, compounds, and substances administered to kill vermin such as bugs, mice, and rats and to repel garden pests such as deer and woodchucks. Examples of suitable pesticides that can be used according to the invention include, but are not limited to, abamectin (acaricide), bifenthrin (acaricide), cyphenothrin (insecticide), imidacloprid (insecticide), and prallethrin (insecticide). Other examples of suitable pesticides for use in the invention are listed in *Crop Protection Chemicals Reference*, 6th ed., Chemical and Pharmaceutical Press, John Wiley & Sons Inc., New York, 1990; (1996) *The Encyclopedia of Chemical Technology*, 18 Kirk-Othmer (4th ed. at 311-341); and Hayes *et al.*, *Handbook of Pesticide Toxicology*, Academic Press, Inc., San Diego, CA, 1990, all of which are incorporated by reference herein.

Herbicides include selective and non-selective chemicals, compounds, and substances administered to kill plants or inhibit plant growth. Examples of suitable herbicides include, but are not limited to, photosystem I inhibitors, such as actifluorfen; photosystem II inhibitors, such as atrazine; bleaching herbicides, such as fluridone and difunon; chlorophyll biosynthesis inhibitors, such as DTP, clethodim, sethoxydim, methyl haloxyfop, tralkoxydim, and alachlor; inducers of damage to antioxidative system, such as paraquat; amino-acid and nucleotide biosynthesis inhibitors, such as phaseolotoxin and imazapyr; cell division inhibitors, such as pronamide; and plant growth regulator synthesis and function inhibitors, such as dicamba, chloramben, dichlofop, and ancymidol. Other examples of suitable herbicides are listed in *Herbicide Handbook*, 6th ed., Weed Science Society of America, Champaign, IL 1989; (1995) *The Encyclopedia of Chemical Technology*, 13 Kirk-Othmer (4th ed. at 73-136); and Duke, *Handbook of Biologically Active Phytochemicals and Their Activities*, CRC Press, Boca Raton, FL, 1992, all of which are incorporated herein by reference.

Fungicides include chemicals, compounds, and substances administered to plants and crops that selectively or non-selectively kill fungi. For use in the invention, a fungicide can be systemic or non-systemic. Examples of suitable non-systemic fungicides include, but are not limited to, thiocarbamate and thiurame derivatives, such as ferbam, ziram, thiram, and nabam; imides, such as captan, folpet, captafol, and dichlofluanid; aromatic hydrocarbons, such as quintozone, dinocap, and chloroneb; dicarboximides, such as vinclozolin, chlozolate, and iprodione. Example of systemic fungicides include, but are not limited to, mitochondrial respiration inhibitors, such as carboxin, oxycarboxin, flutolanil, fenfuram, mepronil, and methfuroxam; microtubulin polymerization inhibitors, such as thiabendazole, fuberidazole, carbendazim, and benomyl; inhibitors of sterol biosynthesis, such as triforine, fenarimol, nuarimol, imazalil, triadimefon, propiconazole,

flusilazole, dodemorph, tridemorph, and fenpropidin; and RNA biosynthesis inhibitors, such as ethirimol and dimethirimol; phospholipic biosynthesis inhibitors, such as ediphenphos and iprobenphos. Other examples of suitable fungicides are listed in Torgeson, ed., *Fungicides: An Advanced Treatise*, Vols. 1 and 2, Academic Press, Inc., New York, 1967 and (1994)

5 *The Encyclopedia of Chemical Technology*, 12 Kirk-Othmer (4th ed. at 73-227), all of which are incorporated herein by reference.

Components to be combined with agrochemicals to form samples include those substances known in the art of agrochemical compounding, for example, inert ingredients, such as solvents, emulsifiers, surfactants, dispersants, stabilizers, preservatives,

10 sequestrates, colors, flavors, and fragrances. Examples of suitable components for samples comprising agrochemicals are listed in Stevens *et al.*, 1993 *Pesticide Science* 38:103-122 and *Adjuvants for Agrochemicals*, ed. C. L. Foy, CRC Press, Boca Raton, Florida, 1992.

In one aspect of the embodiment concerning arrays of samples, wherein the component-in-common is an agrochemical, other agrochemicals are additional components.

15 That is, each sample can comprise multiple agrochemicals, wherein a particular agrochemical is present in all the samples (agrochemical-in-common). An array of such samples can be used to detect a favorable or synergistic interaction between agrochemicals, for example, identification of a pesticide combination that is particularly advantageous due to their interaction with each other. Such advantageous combinations can be unexpected

20 based on the properties of the agrochemicals in isolation.

In another embodiment, the invention relates to a method to measure or detect an interaction between components, comprising:

- (a) preparing an array of samples, each sample comprising an agrochemical-in-common and at least one additional component, wherein each sample differs
- 25 from any other sample with respect to at least one of:
- (i) the identity of the additional component,
 - (ii) the ratio of the agrochemical-in-common to the additional component; or
 - (iii) the physical state of the agrochemical-in-common;
- 30 (b) testing each sample for a property to generate a data set; and
- (c) analyzing the data set to measure or detect the interaction.

Preferably, samples comprising agrochemicals are tested for properties related to the use and administration of agrochemicals. Preferred properties for agrochemicals include biodegradability (*e.g.*, rate of degradation due to chemical instability or microbial

35 metabolism), rate of soil absorption, potency, toxicity, duration of effect, rate of

evaporation. Such properties are directly related to solubility (especially aqueous solubility), partitioning, and physical and chemical stability, which can be measured by the methods discussed above for measuring pharmaceutical formulation properties. One of skill in the art can readily develop assays to measure such properties. For references aiding
5 development of assays related to measuring agrochemical properties see Somasundaram *et al.*, *Pesticide Transformation Products: Fate and Significance in the Environment*, ACS Symposium Series No. 459, American Chemical Society 1991. Tweedy *et al.*, *Pesticide Residues and Food Safety: A Harvest of Viewpoints*, ACS Symposium Series No. 446, American Chemical Society 1991; Van Emon *et al.*, *Immunochemical Methods For*
10 *Environmental Analysis*, ACS Symposium Series No. 442, American Chemical Society 1990; and Cairns *et al.*, *Emerging Strategies for Pesticide Analysis*, CRC Press, Boca Raton, FL 1992; From the series *Modern Methods of Pesticide Analysis*, all of which references are incorporated herein by reference.

15 Consumer and Industrial Product Formulations

In another embodiment, the invention relates to an array of samples, each sample comprising a component-in-common, wherein the component-in-common is an active component of a consumer product formulation or an active component of an industrial product formulation and at least one additional component, wherein each sample differs
20 from any other sample with respect to at least one of:

- (i) the identity of the additional component,
- (ii) the ratio of the component-in-common to the additional component;
- or
- (iii) the physical state of the component-in-common.

25 As used herein, a "consumer product formulation" means a formulation for consumer use, not intended to be absorbed or ingested into the body of a human or animal, comprising an active component. Consumer product formulations include, but are not limited to, cosmetics, such as lotions, facial makeup; antiperspirants and deodorants, shaving products, and nail care products; hair products, such as and shampoos, colorants,
30 conditioners; hand and body soaps; paints; lubricants; adhesives; and detergents and cleaners.

As used herein an "industrial product formulation" means a formulation for industrial use, not intended to be absorbed or ingested into the body of a human or animal. Industrial product formulations include, but are not limited to, polymers; rubbers; plastics;
35 industrial chemicals, such as solvents, bleaching agents, inks, dyes, fire retardants,

antifreezes and formulations for deicing roads, cars, trucks, jets, and airplanes; industrial lubricants; industrial adhesives; construction materials, such as cements.

One of skill in the art will readily be able to choose active components and inactive components used in consumer and industrial product formulations and set up arrays according to the invention for detecting or measuring an interaction between the active components and additional components. Data concerning such interactions can aid in the optimization of consumer and industrial product formulations. Such active components and inactive components are well known in the literature and the following references are provided merely by way of example. Active components and inactive components for use in cosmetic formulations are listed in (1993) *The Encyclopedia of Chemical Technology*, 7 Kirk-Othomer (4th ed. at 572-619); M.G. de Navarre, *The Chemistry and Manufacture of Cosmetics*, D. Van Nostrand Company, Inc., New York, 1941; *CTFA International Cosmetic Ingredient Dictionary and Handbook*, 8th Ed., CTFA, Washington, D.C., 2000; and A. Nowak, *Cosmetic Preparations*, Micelle Press, London, 1991. All of which are incorporated by reference herein. Active components and inactive components for use in hair care products are listed in (1994) *The Encyclopedia of Chemical Technology*, 12 Kirk-Othomer (4th ed. at 881-890) and Shampoos and Hair Preparations in *ECT* 1st ed., Vol. 12, pp. 221-243, by F. E. Wall, both of which are incorporated by reference herein. Active components and inactive components for use in hand and body soaps are listed in (1997) *The Encyclopedia of Chemical Technology*, 22 Kirk-Othomer (4th ed. at 297-396), incorporated by reference herein. Active components and inactive components for use in paints are listed in (1996) *The Encyclopedia of Chemical Technology*, 17 Kirk-Othomer (4th ed. at 1049-1069) and "Paint" in *ECT* 1st ed., Vol. 9, pp. 770-803, by H.E. Hillman, Eagle Paint and Varnish Corp, both of which are incorporated by reference herein. Active components and inactive components for use in consumer and industrial lubricants are listed in (1995) *The Encyclopedia of Chemical Technology*, 15 Kirk-Othomer (4th ed. at 463-517); D.D. Fuller, *Theory and practice of Lubrication for Engineers*, 2nd ed., John Wiley & Sons, Inc., 1984; and A. Raimondi and A.Z. Szeri, in E.R. Booser, eds., *Handbook of Lubrication*, Vol. 2, CRC Press Inc., Boca Raton, FL, 1983, all of which are incorporated by reference herein. Active components and inactive components for use in consumer and industrial adhesives are listed in (1991) *The Encyclopedia of Chemical Technology*, 1 Kirk-Othomer (4th ed. at 445-465) and I.M. Skeist, ed. *Handbook of Adhesives*, 3rd ed. Van Nostrand-Reinhold, New York, 1990, both of which are incorporated herein by reference. Active components and inactive components for use in polymers are listed in (1996) *The Encyclopedia of Chemical Technology*, 19 Kirk-Othomer (4th ed. at 881-904), incorporated

herein by reference. Active components and inactive components for use in rubbers are listed in (1997) *The Encyclopedia of Chemical Technology*, 21 Kirk-Othmer (4th ed. at 460-591), incorporated herein by reference. Active components and inactive components for use in plastics are listed in (1996) *The Encyclopedia of Chemical Technology*, 19 Kirk-Othmer (4th ed. at 290-316), incorporated herein by reference. Active components and inactive components for use with industrial chemicals are listed in Ash *et al.*, *Handbook of Industrial Chemical Additives*, VCH Publishers, New York 1991, incorporated herein by reference. Active components and inactive components for use in bleaching components are listed in (1992) *The Encyclopedia of Chemical Technology*, 4 Kirk-Othmer (4th ed. at 271-311), incorporated herein by reference. Active components and inactive components for use inks are listed in (1995) *The Encyclopedia of Chemical Technology*, 14 Kirk-Othmer (4th ed. at 482-503), incorporated herein by reference. Active components and inactive components for use in dyes are listed in (1993) *The Encyclopedia of Chemical Technology*, 8 Kirk-Othmer (4th ed. at 533-860), incorporated herein by reference. Active components and inactive components for use in fire retardants are listed in (1993) *The Encyclopedia of Chemical Technology*, 10 Kirk-Othmer (4th ed. at 930-1022), incorporated herein by reference. Active components and inactive components for use in antifreezes and deicers are listed in (1992) *The Encyclopedia of Chemical Technology*, 3 Kirk-Othmer (4th ed. at 347-367), incorporated herein by reference. Active components and inactive components for use in cement are listed in (1993) *The Encyclopedia of Chemical Technology*, 5 Kirk-Othmer (4th ed. at 564), incorporated herein by reference.

In another embodiment, the invention relates to a method to measure or detect an interaction between components, comprising:

- (a) preparing an array of samples, each sample comprising a component-in-common, wherein the component-in-common is an active component of a consumer product formulation or an active component of an industrial product formulation and at least one additional component, wherein each sample differs from any other sample with respect to at least one of:
 - (i) the identity of the additional component,
 - (ii) the ratio of the component-in-common to the additional component;
 - or
 - (iii) the physical state of the component-in-common;
- (b) testing each sample for a property to generate a data set; and
- (c) analyzing the data set to measure or detect the interaction.

Preferably, samples comprising the active component of a consumer or industrial product formulation and an additional component are tested for properties related to the use and administration of the consumer or industrial product formulation. Preferred properties for testing samples comprising the active component of an industrial or consumer product formulations include solubility (especially aqueous solubility), biodegradability, partitioning, and physical and chemical stability. Such properties can be measured by adapting the methods discussed above for measuring pharmaceutical formulation properties.

According to the invention described herein, once an ideal formulation is identified, it can be prepared on a bulk scale for use as formulation for delivery of active components, using standard scale-up procedures well known in the art. For example, a promising sample can be scaled up as a pharmaceutical formulation for delivery of pharmaceuticals.

Sample Preparation and Testing Systems

The basic requirements for sample preparation, processing, and testing are: (1) a distribution mechanism to add components to separate sites on an array plate, such as into sample wells. Preferably, the distribution mechanism is automated and controlled by computer software and can vary at least one addition variable, *e.g.*, the identity of the component(s) and/or the component concentration, more preferably, two or more variables. For instance, addition of a pharmaceutical-in-common and excipients to a sample well involves material handling technologies and robotics well known to those skilled in the art of pharmaceutical process manufacturing. Of course, if desired, individual components can be placed into the appropriate well in the array manually. This pick and place technique is also known to those skilled in the art. And (2) a testing mechanism to test each sample for one or more properties. Preferably, the testing mechanism is automated and driven by a computer. Preferably, the system further comprises a processing mechanism to process the samples after component addition. For example, after component addition, the samples can be processed by stirring, milling, filtering, centrifuging, emulsifying, or solvent removal (*e.g.*, lyophilizing) and reconstituting, *etc.* by methods and devices well known in the art. Preferably the samples are processed automatically and concurrently.

Figure 1 is a flow chart depicting preparing an array of samples, processing the samples, analyzing the samples for one or more properties, collecting and storing the data, and analyzing the data, and detecting or measuring an interaction or detecting a lack of an interaction. The first step comprises selecting the component sources 2, *i.e.*, a component-in-common and one or more additional components at one or more concentrations. Next, adding the component-in-common and additional components to a plurality of sample sites,

such as sample wells on a sample plate to give samples then processing the samples by, for example, stirring, milling, filtering, centrifuging, emulsifying, or concentrating and reconstituting to form an array of samples 4. Each sample in array 4 can be tested for one or more properties and the data collected and stored 6 for subsequent data analysis 8 to measure or identify an interaction(s) or detect a lack of interaction(s) 9 between components. For example, a component-in-common, such as a pharmaceutical, and additional components, such as excipients or other pharmaceuticals in different amounts, different pHs, different physical states, can be distributed in liquid or solid form, or combination thereof, into individual sample sites, such as sample wells, thereby forming a sample array. The different samples comprising different combinations can be processed and tested for properties. The data from testing is stored and analyzed, preferably by a computer, to measure or identify interactions between the pharmaceutical-in-common and excipients or other pharmaceuticals. Such interactions can be used to develop optimum formulations to administer the pharmaceutical.

15 The automated distribution mechanism can distribute or add components in the form of liquids, gels, foams, pastes, ointments, triturates, suspensions, or emulsions or solids, such as powders, tablets, or pellets. Preferably, solids are in the form of micropellets or microtablets, prepared by micropelleting or microtableting. Micropellets can be prepared using standard pharmaceutical tableting machines, modified as appropriate. Such machines are well known in the art, for example, see *Remington's Pharmaceutical Sciences*, 18th Edition, ed. Alfonso Gennaro, Mack Publishing Co. Easton, PA, 1995, Chapter 92, incorporated herein by reference. Preferably, the tableting machine comprises a small die, of from about 1/16" to about 3/16" in diameter. Any required modifications are easily made by those skilled in the art. With the appropriate modification, the microtableting machine can make microtablets of almost any solid component. When the component is an active component, such as a pharmaceutical, preferably, it is dispersed within a matrix of a compressible, inert carrier material, such as potassium chloride. Preferably, the ratio of active component to carrier is about 0.5 to about 10 parts active component to about 90 to about 99.5 parts of carrier, more preferably, about 1 part active component to about 99 parts of carrier. Preferably, the finished microtablets weigh from about 0.1 to about 50 milligrams, more preferably, from about 1 to about 10 milligrams, most preferably, about 5 milligrams. It is also preferable that the finished microtablet contain from about 1 to about 100 micrograms of the active component, more preferably, from about 10 to about 75 micrograms, and most preferably, they contain about 50 micrograms. When the component

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is an inactive component, such as an excipient, it can be dispersed within an inert matrix as just described or pelleted in the absence of an inert carrier.

Another non-limiting method of forming micropellets involves forcing a paste comprising a component and an inert carrier into a mold, drying the paste, and then ejecting the pellet. In this method, the component to be pelleted is first homogenized with an inert carrier and a solvent. Preferably, the inert carrier is lactose or mannitol. Any solvent is suitable and readily selected by one skilled in the art depending on the component. Preferably, the solvent is relatively volatile, more preferably having a boiling point of about 100 °C or less, for example, alcohols such as methanol or ethanol. Preferably, the ratio of solvent to active component/inert carrier mixture is of from about 10:1 to about 1:10, more preferably about 6:1 to about 1:1, even more preferably, from about 5:1 to about 3:1. The component, solvent, and inert carrier are homogenized to a paste and the solvent is then removed at reduced pressure to yield a dry powder. The powder is then mixed with another solvent, preferably water, to form a homogeneous paste, which paste is forced into individual tube shaped molds. Preferably, the dimensions of the molds is from about 1/16" to about 3/16" in depth, preferably, about 1/8" in depth and from about 1/32" to about 1/8" in inner diameter, preferably, about 5/64" inner diameter. The pastes are allowed to dry for about 1 minute to about 5 hours, preferably, for about 5 minutes to about 1 hour, more preferably, for about 10 minutes; at a temperature of from about 15 °C to about 100 °C, more preferably, from about 20 °C to about 30 °C; at a pressure of from about 10 mm/Hg to about 1000 mm/Hg, preferably, at about 20 mm/Hg. Preferably, the paste-in-mold is allowed to dry for about 10 minutes, at about room temperature, and at about atmospheric pressure. The dried paste in the form of a micropellet is then ejected from the molds, preferably, by inserting a flat head pin through the mold, the pin being of about the same diameter, preferably of just a slightly smaller diameter than the inner diameter of the mold. The molded micropellets can then be dried under reduced pressure, preferably, for from about 6 to about 24 hours, more preferably, about 12 hours; at a temperature of from about 15 °C to about 100 °C, preferably at about room temperature; and at a pressure of from about 10mm/Hg to about 1000 mm/Hg, preferably, about 20 mm/Hg.

A preferred automated mechanism for adding solid components, preferably micropellets, to sample wells, comprises reservoirs or bins, for each component. The outlet of these bins is controlled so that an individual microtablet is "singulated" and able to be dispensed to a specified sample well in an array. Once the components and the component-in-common are placed in the sample wells of the array, the assay process continues as outlined below.

Figures 2A and 2B are detailed schematics exemplifying a system of the invention for preparing an array of samples by depositing components into sample wells, processing the samples, testing the samples for one or more properties to generate data, and collecting, storing, and analyzing the data to measure or detect interactions or detect a lack of interactions. Figures 2A and 2B are directed to low-water-solubility pharmaceuticals as the component-in-common and to excipients as the additional components, however, the systems and methods depicted in Figures 2A and 2B apply equally to all the active and inactive components discussed herein.

Figure 2A depicts a system where an solid component-in-common source 10, such as a solid-pharmaceutical source and an solid-component source 12, such as a solid-excipient source are automatically distributed, preferably in micropellet form, to sample sites, such as sample wells in a 96 well filter plate (commercially available, for example, from Millipore, Bedford, MA) to give a plurality of dry samples 14. The combinations of the component-in-common and various components at various combinations are generated using standard software (*e.g.*, Matlab software, commercially available from Mathworks, Natick, Massachusetts). The combinations thus generated can be downloaded into a spread sheet, such as Microsoft EXCEL. From the spread sheet, a worklist can be generated for instructing the automated distribution mechanism to prepare an array of samples according to the various combinations generated by the formulating software. The worklist can be generated using standard programming methods according to the automated distribution mechanism employed. The use of so-called worklists simply allows a file to be used as the process command rather than discrete programmed steps. The worklist combines the formulation output of the formulating program with the appropriate commands in a file format that directly readable by the automatic distribution mechanism.. The automated distribution mechanism delivers at least one component-in-common, such as a pharmaceutical, as well as various additional components, such as excipients, to each sample well. Preferably, the automated distribution mechanism can deliver multiple amounts of each component. Automated liquid distribution mechanisms are well known and commercially available, such as the Tecan Genesis, from Tecan-US, RTP, North Carolina. Automated solid distribution mechanisms are readily obtained by modifying commercially available robotics systems. The plurality of dry samples 14 thus formed are mixed with one or more solvents using the Tecan automated liquid pipetting system thereby providing an array of samples 20, wherein each sample comprises a solution or a suspension. During or after solvent addition, the samples may be mixed or agitated, preferably, however, the force of the liquid addition provides adequate mixing. If desired,

suspensions can be filtered to separate the solid and liquid phases thus forming an array of filtrates 22. To accomplish filtration, the filter plate comprising the suspension is placed on top of a receiver plate containing the same number of sample wells, each of which corresponds to a sample well on the filter plate. By applying either centrifugal or vacuum force to the filter plate over receiver plate combination, the liquid phase of the filter plate is forced through the filter on the bottom of each sample well, into the corresponding sample well of the receiver plate. The appropriated centrifuge is available commercially, for example, from DuPont, Wilmington, DE. The receiver plate is designed for analysis of the individual filtrate samples.

Analysis of the filtrates can provide data concerning the component solubility using devices 24, such as UV-Vis spectroscopy (using plate-based readers known to those skilled in the art, an example of which is the SpectraMax Plus from Molecular Devices, Sunnyvale, CA), GC, HPLC, and LC-MS. In the case of GC, HPLC, and LC-MS, an automated pipetting station is used for sample introduction, for example, the Genesis from Tecan or any of several devices sold by Gilson, Middleton, WI). Analytical devices used to measure stability 26 include, but are not limited to, UV-Vis spectroscopy, MS, GC, HPLC, or LC-MS. These devices are also modified for use with the array as previously discussed. Analytical devices for measuring absorption 28 include the Caco-2 cell line or Ussing Chambers. The Caco-2 cell line is known to those skilled in the art to be a surrogate for intestinal permeability measurements. There are analysis devices sold specifically for absorption assay, namely those sold by Tecan-US (Cell-growth and Cell-feeding platforms). Ussing chambers are widely used by those skilled in the art to measure intestinal permeability of compounds. There are commercially available devices, such as those sold by World Precision Instruments, Sarasota, Florida, for measuring absorption. Systems for measuring metabolism 30 include P-450, microsomes and lysosomes, obtainable from companies such as In Vitro Technologies, 1450 South Rolling Road, Baltimore, MD 21227; see also; Trouet A *et al.*, *Methods in Enzymology*, Vol. 31, Academic Press, Inc., New York, 1987, pp. 287-313 and 323-329) and *in vivo* assays. Other analytical devices that can be used with the methods and arrays of the invention include pH sensors, ionic strength sensors, optical spectrometers, devices for measuring turbidity, calorimeters, infrared spectrometers, polarimeters, radioactivity counters, conductivity measurers, and heat of dissolution measurers. The property-test data is collected and stored 32 then analyzed 34 to detect or measure interactions 36.

Data collection and storage 32 preferably, are performed by computers using the appropriate software. Such computers and software for data collection and storage are

readily chosen by one of skill in the art. The samples are first analyzed using the appropriate equipment, as just discussed, for the property under study to generate a data set. For example, a UV spectrophotometric analysis of each sample can be obtained using a Spectramax Plus™ spectrophotometer available from Molecular Devices, Sunnyvale, CA.

- 5 The data is typically collected and stored using software provided by the instrumentation manufacturer. For example, the data collected by the Spectramax is collected and stored using Softpro™ from Molecular Devices. The data set can then be downloaded to a database for analysis.

- Data analysis 34 can be performed using visualization software, such as SPOTFIRE (commercially available from Spotfire, Inc., Cambridge, MA). The visualized data can be analyzed directly to arrive at optimized formulations and interactions 36. Or the data can be processed through data mining algorithms so as to optimize the ability of scientific personnel to detect complex multi-dimensional interactions or lack of interactions between components or to conduct future experiments to optimize the formulations. Examples of suitable data-mining software include, but not limited to, SPOTFIRE; MATLAB (Mathworks, Natick, Massachusetts); STATISTICA (Statsoft, Tulsa, Oklahoma). All resulting analysis files are stored on a central file server, *i.e.*, a data base, where the files can be accessed by traditional means known to those skilled in the art.
- 15

- Figure 2B shows essentially the same process but for liquid components-in-common 38, such as liquid pharmaceuticals and liquid component(s) 40, such as liquid excipients. Such liquid components can be dispensed using an automated liquid distribution mechanism to make the sample array 42. The solvent is then removed at reduced pressure or by evaporation to give an array of dried samples 44. Lyophilization or other solvent removal procedures, are readily adapted to arrays 42 by those skilled in the art.
- 25 Commercially available lyophilization devices that can be used without modification. The array of dried samples 44 can be reconstituted to an array of reconstituted samples 46 by adding one or more component solvents using an automated liquid pipetting device, as previously described. The array of reconstituted samples 46 can then be analyzed as discussed above for Figure 2A, by.

- 30 Although the present invention has been described in considerable detail with reference to certain preferred embodiments, other embodiments are possible. Therefore, the spirit and scope of the appended claims should not be limited to the description of the preferred embodiments contained herein.

35 EXAMPLES

The present invention will be further understood by reference to the following non-limiting example of the arrays and methods disclosed herein. The following examples are provided for illustrative purposes only and are not to be construed as limiting the invention's scope in any manner.

- 5 Griseofulvin, a commercial antibiotic having a complex derivatized benzofuran-cyclohexane structure, was selected as the component-in-common for use in an array to identify excipient combinations that solubilize the pharmaceutical in aqueous medium more effectively than the present commercial griseofulvin formulation. The compound is marketed for oral administration. A dosage of 3.3 milligrams/lb body weight is
- 10 administered per day for children under 50 lbs and 330 milligrams/day is the typical dosage for adults. The selected compound is practically insoluble in water, slightly soluble in polar organic solvents such as ethanol, methanol, acetone and acetic acid, and soluble in dimethylformamide and dioxane. The low-water solubility limits the bioavailability. The commercially available preparation, used as a standard, consists of ultramicrosized crystals
- 15 of the compound partially dissolved in a carrier including polyethylene glycol 8000 and partially dispersed in other inert excipients (corn starch, lactose, magnesium stearate, and sodium lauryl sulfate).

- Using the methods of the invention, an array of samples, each containing griseofulvin and various excipient mixtures were rapidly prepared and systematically
- 20 analyzed to identify excipient combinations that interact with each other and with the compound to provide aqueous solubility enhanced over the commercial formulation.

The following GRAS ("generally regarded as safe") excipients (all obtainable from Sigma-Aldrich Fine Chemicals or BASF) listed in Table 2 below, were used as excipients in the following examples.

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Table 2: Excipients Used in the Examples

- 10390
092267-072800
- | | | |
|----|------|--|
| | (1) | gum arabic from acacia tree (a branched polymer of galactose, rhamnose, arabinose, and glucuronic acid, mw approximately 25,000) |
| 5 | (2) | β -cyclodextrin (cycloheptaamylose), |
| | (3) | sodium dodecyl sulfate (SDS) |
| | (4) | sodium docusate (sulfobutanedioic acid bis[2-ethyl-hexyl ester] or dioctyl sulfosuccinate) |
| 10 | (5) | sodium benzethonium chloride |
| | (6) | benzalkonium chloride (alkyldimethylbenzylammonium chloride) |
| | (7) | cetrimide (dodecyltrimethylammonium bromide) |
| | (8) | oleic acid (cis-9-octadecenoic acid) |
| 15 | (9) | sodium tartrate dihydrate |
| | (10) | polyethylene glycol 1000 |
| | (11) | polyethylene glycol 10,000 |
| | (12) | polyvinyl alcohol |
| | (13) | POLOXAMER® 237 (polyoxyalkylene oxide block copolymer) |
| 20 | (14) | polyoxyethylene 40 stearate |
| | (15) | polyoxyethylene 100 stearate |
| | (16) | TWEEN 80® (polyoxyethylenesorbitan) |
| | (17) | BRIJ 35® (23 lauryl ether) |
| 25 | (18) | BRIJ 97® (10 Oleyl ether) |

The samples were prepared, processed, and analyzed as demonstrated by the following examples.

30

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EXAMPLE 1: Preparation and Identification of Griseofulvin Formulations with Enhanced Solubility.

Preparation of formulations with improved solubilities

5 Each of the 18 excipients were prepared as three aqueous stock solutions at different concentrations, *i.e.*, 0.015 milligrams/milliliter, 0.15 milligrams/milliliter, and 1.5 milligrams/milliliter, to give a total of 54 stock solutions. To each sample well was added three different excipients, each excipient chosen from one of its respective three stock solutions. Thus, three of the 18 excipients listed above, 20 micro liters each, were added to
10 each sample well in the array (Millipore 96 well filter plates, with a volume of 250 μ l, including one micron pore size polytetrafluoroethylene membranes in the bottom of each well using the TECAN® liquid handling device using the Genesis liquid handling device (Tecan-US, RTP, NC). The number of possible unique combinations of 3 different excipients, each excipient chosen from three different-concentration stock solutions is
15 calculated as:

$$\frac{18!}{3! \times (18-3)!} \times 3^3$$

70400
0962857-072800

Giving a grand total of 22,032 unique samples (a total of 66,096 samples for $n=3$) were
20 generated, with 32 unique samples per assay plate and 689 assay plates in total. All permutations of excipients, concentrations, and griseofulvin according to the above equation were generated using the MatLab program formulating software. The permutations so generated were down loaded into a Microsoft EXCEL spread sheet and from this spread sheet, a worklist was constructed according to standard programming methods well known
25 to those skilled in the art. The work-list is then used to direct the automated distribution mechanism to prepare the various permutations of excipients and griseofulvin generated by Matlab. The Genesis liquid handling device was used as the automated distribution mechanism. The worklist combines the formulation output of the Matlab program with Genesis-appropriate commands (as found in the Genesis operating manual) in a file format
30 this is directly readable by the Genesis device. Thus, the Genesis liquid handling device delivered 20 micro liters of a griseofulvin/dioxane solution (0.15 milligrams griseofulvin/milliliter dioxane) and the various combinations and concentrations of excipients generated by the Matlab program to each sample well. The force provided by adding the excipient was enough to adequately mix the components.

35

Testing of Samples

All the solvents were removed by lyophilization then water (200 µl) was added to each dried well of the filter plates, again using the Genesis liquid handling device. The plates were the incubated at 37 °C for 1 hour in a Innova 4200 incubator (New Brunswick Scientific, Edison, NJ). The plates were then centrifuged to separate any undissolved solids, as previously described. The centrifuge was a Sorvall RT6000B (DuPont, Wilmington, DE). The filtrate from each well was collected into UV transparent 96 well receiver plates (Corning, Corning, NY) for measurement on a UV plate reader at 290 nm (SpectraMax Plus, Molecular Devices, Sunnyvale, CA).

Griseofulvin alone without any excipient was tested to establish the baseline solubility.

Results

The solubility, measured as absorbance at 290 nm of the filtrates, for 3,500 unique samples is shown in Figure 3A. The commercial griseofulvin preparation FULVICIN, Schering-Plough) alone gave a baseline absorbance (solubility) of 0.3 absorbance units. Most samples showed improved solubility compared to the commercial griseofulvin preparation. Approximately 1,200 samples shown in Figure 3A showed significantly higher solubilities than the rest of the samples.

Samples demonstrating 100% increase in solubility compared to griseofulvin alone (as measured by absorbance) were identified as lead formulations. Five samples were identified and boxed in Figure 3A. The compositions of the 5 lead formulations (TP1-TP5) are listed in Table 3 below.

TABLE 3: 5 Lead Formulations for Solubilizing Griseofulvin

	TP1		TP2		TP3		TP4		TP5	
	Excipient	wt %	Excipient	wt %	Excipient	wt %	Excipient	wt %	Excipient	wt %
30	(10)	83.3	(10)	90%	(10)	90%	(11)	83.3	(12)	90%
	(2)	8.3 %	(3)	1%	(14)	9%	(1)	8.3%	(5)	9%
	(14)	8.3%	(14)	9%	(1)	1%	(7)	8.3%	(10)	1%

Figure 3B gives the standard deviation for each of the 3,500 unique samples (each tested at n = 3). The majority of the samples tested were reproducible, with standard deviations of less than 10%.

These samples can be further optimized using the same testing technique described above, by making additional changes to the concentration of each component in the samples.

5 EXAMPLE 2: Validation of Lead Formulations on a Larger Scale.

The five lead formulations identified from the Example above were validated on a lab scale 10,000 times that of the microarray in 96 well plates by weighing each component and mixing them in the solid state in scintillation vials. Griseofulvin (30 milligrams) was weighed into each formulation. Each formulation was formulated three times.

10

Formulations

TPI-1: 300 milligrams PEG 1000, 30 milligrams beta-cyclodextrin, 30 milligrams polyoxyethylene 40 stearate

TPI-2: 300 milligrams PEG 1000, 30 milligrams SDS, 3 milligrams polyoxyethylene 40

15 stearate

TPI-3: 300 milligrams PEG 1000, 30 milligrams polyoxyethylene 40 stearate, 3 milligrams acacia

TPI-4: 300 milligrams PEG 10000, 30 milligrams acacia, 30 milligrams cetrimide

TPI-5: 300 milligrams polyvinylalcohol, 30 milligrams benzethonium chloride, 3

20 milligrams PEG 1000

15 milliliters water was added to each vial and the formulations incubated at 37°C for 1 hour before they were filtered through 0.2 micron filters to remove any undissolved solids. The filtrates were measured using a UV spectrometer at 290 nm in a 1 cm path-length quartz cuvette.

25 The commercially available FULVICIN (having 165 milligrams griseofulvin) in tablet form was ground into powder and an amount containing 30 milligrams griseofulvin was tested in the same way as the lead formulations for comparison.

Results

30 The results from the lab scale dissolution assay are plotted in Figure 4 as absorbance at 290 nm, showing the means and standard deviations from the three measurements. An increase of up to 300% in solubilities (as measured by UV) was achieved compared to the commercial formulation. All five lead formulations identified in the microarray test were validated in the solid form in the lab scale (10,000x) dissolution assay to have increased

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solubility compared to the commercially available pharmaceutical, proving the results from microarray assay format can now be translated into normal lab scale assays.

EXAMPLE 3: Evaluation of Individual Effect of Each Excipient.

5 To examine the effect of each excipient on griseofulvin's solubility, the first three lead formulations (TPI-1 to TPI-3) identified above in the micro arrays described above were "de-convolved" on the lab scale into griseofulvin formulations that contain (1) one of the three excipients only, or (2) two of the three excipients in different combinations (example, components one and two, two and three, one and three). Solubilities of each sample were
10 then measured using the same lab procedures described above for lead validation, using absorbance at 290 nm to determine solubility.

The solubilities for the "de-convolved" formulations are shown in Figure 5, 6 and 7 as ratios to their respective lead formulation (It is important to note that some reformulations have greater or less solubilities than the lead formulations identified in
15 Example 1, but that the results are relative to the starting lead formulation; not absolute absorbance).

In Figure 5, excipient 14 (polyoxyethylene 40 stearate) (which is present as a small percentage in TPI-3, as indicated by the area in the pie chart) yields a substantial increase in solubility, which was slightly enhanced by excipient 10 (PEG 1000). Thus, a positive
20 solubility interaction was identified between excipient 14 and griseofulvin.

As shown by Figure 5, 14 (polyoxyethylene 40 stearate) was the only important excipient in TPI-3 and addition of 10 (PEG 1000 and 1 (acacia) had no effect on overall solubility. Addition of excipient 2 (β -cyclodextrin) actually decreased overall solubility of the griseofulvin in TPI-1, as shown in Figure 6, demonstrating an antagonistic solubility
25 interaction among excipients.

In contrast, as shown by Figure 7, excipient 3 (SDS), 10 (PEG 1000), and 14 (polyoxyethylene 40 stearate) show a synergistic solubility interaction in enhancing solubility of griseofulvin.

30 EXAMPLE 4: Dissolution Rate Comparison under Simulated USP Conditions

The rates of dissolution of TPI-2 and the commercial griseofulvin formulation (165 milligrams) were compared at the lab scale using 1000 milliliters deionized water in 1000 milliliters Erlenmeyer flasks at 37°C stirred at 300 RPM with a 1.5 inch magnetic stir bar. The rate of dissolution for each formulation was determined separately. Each formulation
35 was added to the stirring deionized water and 1 milliliter aliquots were removed at 0

seconds, 30 seconds, 1 minute, 3 minutes, 6 minutes, 10 minutes, 15 minutes, 25 minutes, 40 minutes, and 50 minutes. Each aliquot was added to a 1.5 milliliters Eppendorf vial, centrifuged at room temperature at 14,000 RPM for 10 seconds to remove undissolved solids and the ultraviolet absorbance determined at 290 nm in a 1 cm path-length quartz
5 cuvette.

Results

The rates of dissolution are shown in Figure 8. TPI-2 showed a faster rate of dissolution as well as a higher equilibrium solubility compared to the commercial
10 preparation FULVICIN, further confirming the validity of the lead formulations selected from the micro arrays.

These results demonstrate the efficacy of the high throughput formulation and testing methods, and how it is possible to scale up the results with a high degree of reproducibility.

15 The foregoing has outlined rather broadly the more pertinent and important features of the present invention. While it is apparent that the invention disclosed herein is well calculated to fulfill the objects stated above, it will be appreciated that numerous modifications and embodiments may be devised by those skilled in the art. Therefore, it is intended that the appended claims cover all such modifications

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